

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/26, 38/31	A1	(11) International Publication Number: WO 99/64060 (43) International Publication Date: 16 December 1999 (16.12.99)
(21) International Application Number: PCT/SE99/00997 (22) International Filing Date: 8 June 1999 (08.06.99) (30) Priority Data: 9802080-3 11 June 1998 (11.06.98) SE (71)(72) Applicants and Inventors: HELLSTRÖM, Per [SE/SE]; Svärdsjövägen 1, S-167 75 Bromma (SE). EFENDIC, Suad [SE/SE]; Stjärnvägen 16B, S-181 34 Lidingö (SE). (74) Agents: FOGELBERG, Lennart et al.; Allied Attorneys Chemical AB, P.O. Box 24107, S-104 51 Stockholm (SE).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF FUNCTIONAL DYSPEPSIA AND/OR IRRITABLE BOWEL SYNDROME AND NEW USE OF SUBSTANCES THEREIN		
(57) Abstract The invention relates to the new use of gastrointestinal peptide hormones selected from the class consisting of glucagon-like peptide-1 (GLP-1) and derivatives thereof having anti-secretory effects and smooth muscle relaxatory properties in the gastrointestinal tract for the manufacture of a pharmaceutical composition for the treatment of functional dyspepsia and/or irritable bowel syndrome. The invention also relates to a pharmaceutical composition comprising a combination of at least one member selected from said class consisting of GLP-1 and derivatives thereof with one or more other gastrointestinal peptide hormone(s) or derivative(s) thereof together with pharmacologically acceptable additives and to a method of treating functional dyspepsia or irritable bowel syndrome or both by administering an effective amount of at least one member of said class consisting of GLP-1 and derivatives thereof having effects and properties as mentioned above.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF FUNCTIONAL DYSPEPSIA AND/OR IRRITABLE BOWEL SYNDROME AND NEW USE OF SUBSTANCES THEREIN.

5 The present invention relates to a new use of a gastrointestinal peptide hormone or a derivative thereof, to a pharmaceutical composition for the treatment of functional dyspepsia and/or irritable bowel syndrome, and to a method for such treatment.

10

Functional diseases are characterized by disordered function of the organ or organ system and no obvious structural pathology can be detected neither macroscopically nor microscopically. This should be differentiated from morphologic pathological diseases where the structure of the organ is changed from normality to abnormality. This type of disease can always be diagnosed either macro- or microscopically, and may be followed by functional aberration of the organ.

20 In the gastrointestinal tract the two most common functional disorders are functional dyspepsia and disordered gastrointestinal motility, commonly known as irritable bowel syndrome (IBS). These two terms are not exclusive determinants for separate disease entities, but instead the most common expressions for various overlapping symptoms emerging from the upper and lower gastrointestinal tract.

30 Abdominal pain or discomfort is remarkably common in the general population. The annual prevalence of recurrent abdominal pain or discomfort in Western countries is approximately 25 %. If frequent heartburn with retrosternal burning pain or discomfort is also considered the prevalence approaches 40 % (Locke et al, 1997; Agréus and Talley, 1997; Talley et al, 1992).

35 The term dyspepsia refers to chronic or recurrent pain or discomfort centered in the upper abdomen. The major organic diseases that cause dyspepsia are gastroduodenal ulcer, gastoesophageal reflux and gastric cancer. Up to 60 % of pa-

-2-

tients with dyspepsia have no definite explanation for their symptoms and are classified as having functional dyspepsia. These patients may respond to reassurance and explanation of the background to their symptoms, and at times anti-secretory or motility regulatory pharmacotherapy. Even though the bacteria *Helicobacter pylori* may be encountered in patients with functional dyspepsia, it is yet not recommendable to pursue eradication therapy unless a peptic ulcer is found, and is often of limited value in relieving symptoms. In patients with persistent symptoms, other treatments that may be considered include behavioral therapy, psychotherapy, or antidepressant therapy, but these approaches are not of established value.

The management of dyspepsia represents a major issue in clinical practice; 2-5 % of all general practice consultations are accounted for by dyspepsia. Yet, as no obvious cause for the disease is at hand, treatment strategies have to be empirical; either aiming at anti-secretory or motility regulatory therapeutic measures.

20

Among different treatment strategies available for functional dyspepsia these include: motility regulatory agents, antacids, H₂-receptor antagonists and, often prokinetics.

25

Gastrointestinal motility disorders are considered a common cause of functional dyspepsia. In cases of slow gastric emptying, motility stimulating agents, so-called prokinetics such as metoclopramide (Albibi et al, 1983) and cisapride (Rebois et al, 1984; Delattre et al, 1985; Rösch, 1987; Abell et al, 1990), have been tried with reported symptomatic relief. In spite of this observation there is an undefined relationship between slow gastric emptying and symptoms and it is therefore unclear if the observed symptomatic relief depends on normalization of gastric emptying rate. Recent clinical trials with cisapride have disclosed symptomatic relief in 60-90 % of the studied patients with dysmotility-like and gastroesophageal reflux-like dyspepsia, which should be compared to a 5-60 % relief in placebo-treated groups (Talley

-3-

1991). Treatment with prokinetic drugs may thus be worthwhile, but does not resolve the problem.

Antacids have generally been considered as potentially effective in treatment of dyspeptic symptoms. No reliable data are available on their efficacy in functional dyspepsia (Talley, 1991), and antacids may rather be used as an on-demand treatment than continuous medication against functional dyspepsia.

10 H₂-receptor antagonists, such as cimetidine and ranitidine, have been studied in the treatment of functional dyspepsia. About half of the reported studies show paucity of therapeutic response, whereas others have found statistic evidence for a therapeutic response to H₂-receptor antagonist therapy (Talley, 1991). Mainly, patients with ulcer-like symptoms in the form of burning epigastric pain, may gain some symptomatic relief (Delattre et al, 1985) with H₂-receptor antagonists. In addition to this, it is an every day experience that patients may benefit from an even more profound anti-
15 secretory treatment by the use of a proton pump inhibitor such as omeprazole, lansoprazole or pantoprazole.
20

Thus, some symptomatic relief may be achieved with agents that inhibit gastric acid secretion.

25

IBS is common and involves about 1-2 % of the population and accounts for up to one third of doctor's visits in general practice. The disease seems to be life-long with continuous relapsing activity, but it has not yet been studied how the
30 disease affects the subject over a life span. No effective treatment is yet available. One major obstacle for the development of an effective drug is the fact that no reliable diagnostic hallmark of the disease is at hand, and for diagnostic purposes the doctor has to rely on the patient's case
35 history and subjective reports, mainly as pain episodes and variable bowel habits.

- 4 -

During symptomatic periods a pattern of hypermotility, consisting of high-amplitude pressure waves are ten times as common in pain-dominant IBS than in normal subjects, whereas patients with the diarrhea-predominant disorder have normal or lower than normal pressure waves. These observations fit with basic data from recordings of colonic motility of normal subjects and patients with constipation or diarrhea. Such studies have demonstrated that the predominant form of motor activity from the colon consists of segmental contractions, which impede the propulsion of stool and promote mixing and absorption of water. These segmental contractions appear for more than 90 % of the recorded time. Augmentation of segmental contractions produces constipation and inhibition of segmentation motor activity produces diarrhea. Studies indicate that contractions over a long segment of the colon may be accompanied by abdominal pain, analogous to diffuse esophageal spasm, the nutcracker syndrome of the esophagus and chest pain. Such high-amplitude contractions over long segments of the gut are often recorded in patients with IBS under episodes of crampy abdominal pain, i.e. the "gut-cracker syndrome". Hypermotility of the small intestine also has been found in association with pain. Anecdotal evidence speak in favor of spasmodic cramping as the major source of symptoms in irritable bowel syndrome. Thus, regarding the pathophysiology of irritable bowel syndrome, disordered gastrointestinal motility or disturbances in the sensory system, or both, are suggested to be most important factors. However, there are many reports demonstrating disturbed small intestinal motility in patients with IBS in terms of the migrating motor complex activity. In the fasted state this activity includes phase I, displaying quiescence with no motor activity, phase II with sporadic contractions that become more intense over time and precede the characteristic phase III with high amplitude contractions to a level of about 40-50 mm Hg. In irritable bowel syndrome, increased phase II contraction frequency, increased contraction amplitude, and increased clustered contractions have been described (Kellow et al, 1987; Kellow et al, 1990; Lind, 1991; Kellow et al, 1992; Schmidt

-5-

et al, 1996; Evans et al, 1996; Small et al, 1997). Radiologic studies demonstrate small bowel motor hyperactivity under stress and support the contention that IBS can involve also other parts of the gastrointestinal tract than the colon. Reports also exist which fail to detect any disturbance in intestinal motility in patients with IBS (Gorard et al, 1994).

A number of studies point in favor of sensory disturbances, such as mechanoreceptor hypersensitivity (Kellow et al, 1988; Evans et al, 1996) and an increased awareness of intestinal distension and contractions (Kellow et al, 1992).

According to the present invention it has now surprisingly been found that the disturbances characterizing functional dyspepsia and/or IBS can be normalized by the administration of certain substances which combine anti-secretory effects with smooth muscle relaxatory properties (i.e. motility inhibiting rather than motility stimulating effects).

A great number of peptides have been disclosed in the gastrointestinal tract during the last 25 years. Some of these peptides are considered endocrine in their action as they are located within mucosal cells of the "open type" reaching the lumen with their apical surface and the wide-based bottom towards the blood vessels permitting a release of peptides to the circulation. The peptides are regularly stored within dense large granulae, which can be depleted in exchange for ionized calcium. The peptides released to the blood stream may act as hormones at sites distant from their release or locally as paracrine substances. Their actions may be involved in the control of different gastrointestinal functions such as absorption, secretion, blood flow and motility.

A number of gastrointestinal peptide hormones have both anti-secretory effects and smooth muscle relaxatory properties in the gastrointestinal tract. A especially potent and thereby interesting peptide hormone of this category is glucagon-like peptide-1 (GLP-1).

- 8 -

The term "an effective amount" as used in the description and the claims is intended to designate a dose which causes a marked relief of the symptoms.

- 5 As is generally perceived by the man of ordinary skill in the art the dosage will vary depending on the administration routes, symptoms and body weight of the patient but also depending on GLP-1 or derivative thereof being administered.
- 10 In case of injections the dose of GLP-1 is generally within the range of 40-200 pmol/kg body weight/h, preferably 70-150 pmol/kg body weight/h. In combination with somatostatin, a dose of 2-15 µg/kg body weight/h, preferably 4-7 µg/kg body weight/h of somatostatin should be used.
- 15 The administration frequency can suitable be selected within the range from once to four times a day.
- 20 The invention will now be further illustrated by means of an Example, which illustrates the best mode contemplated at present for carrying out the invention.

Example

Decrease of small bowel motility in humans with IBS

- 25 Experiments were carried out in 12 subjects fulfilling the Rome-criteria for IBS. In the fasted subjects a small bowel manometry tube was passed through the nose and located in antroduodenal region under fluoroscopy. Then, small bowel manometry was recorded for 8 hours in the fasted state, and for an additional 40 min after a meal (320 kcal). During the first 4-hour period of the recording saline was administered intravenously. During the second 4-hour period GLP-1 was given intravenously either at a dose of 1.2 pmol/kg/min (72 pmol/kg/h) (n = 6) or 2.5 pmol/kg/min (150 pmol/kg/h) (n = 6) with the infusion continued over the 40-minute meal period.

- 9 -

GLP-1 was administered as an intravenous infusion at a dose of 1.2 or 2.5 pmol/kg/min. The compound was diluted from a stock solution of GLP-1 (Polypeptide, Wolfenbüttel, Hannover, Germany) 100 nmol/ml prepared according to general guidelines 5 with sterilization filtration and endotoxin test, and divided in 10 ml ampoules.

For each patient the solution for infusion was constituted according to body weight. The dose to be given was multiplied 10 by body weight, resulting in an individual dosing, expressed as pmol/min. The calculated total dose (according to extrapolated 250 ml infusion time) was taken from the stock solution and diluted in 250 ml infusion volume of saline (Natriumklorid 9 mg/ml, Pharmacia & Upjohn, Stockholm, Sweden). The infusion was then given at a rate of 1 ml/min with a constant 15 infusion pump (Volumetric infusion pump, model 960, Imed, Oxon, UK) over 4 hours (240 min).

The overall result showed that GLP-1 was able to reduce the 20 motor activity in IBS patients. However, within 14.2 ± 3.8 min after onset of GLP-1 infusion at 1.2 pmol/kg/min, and within 12.0 ± 2.7 min after onset of GLP-1 infusion at 2.5 pmol/kg/min, an MMC was started in the duodenum in four out of six patients in each group. As this premature MMC cycle was considered to 25 be due to an immediate effect of GLP-1 during a build-up of a steady state concentration in the circulation, an adjusted MMC prevalence during GLP-1 infusion was calculated by subtracting the premature MMC at onset from the remaining MMC observed during infusion of GLP-1.

30

In detail, the following results were obtained from the motility recordings (reference point: angle of Treitz; values are mean \pm SEM of n = 6 in each group; statistical evaluation by the non-parametric Wilcoxon signed-rank test):

35

-10-

Dose	Saline	GLP-1 1.2 pmol/kg/min	Saline	GLP-1 2.5 pmol/kg/min
Contraction frequency (#/min)	1.7 ±0.2	1.7 ±0.4	2.0 ±0.3	0.9 ±0.2 (p<0.031)
Contraction amplitude (mm Hg)	26.7 ±2.7	24.7 ±1.6	30.7 ±2.8	23.6 ±2.5 (p<0.062)
Contraction area (mm Hg*s)	39.1 ±5.0	33.4 ±3.2	47.9 ±5.9	30.5 ±5.3
Motility index Ln (Sum(mm Hg*s)/min)	4.9 ±0.2	4.7 ±0.3	5.3 ±0.2	3.8 ±0.8
Adjusted MMC (#/4 h)	1.3 ±0.5	0.0 ±0.0 (p<0.062)	1.0 ±0.5	0.2 ±0.2 (p<0.062)

= number; MMC = migrating motor complex

In summary, in the fasted state GLP-1 exhibits a dose-dependent reduction of motor activity in the small bowel in patients suffering from irritable bowel syndrome. In conclusion this implies that GLP-1 may be used as a therapeutic agent for symptomatic relief in cases with functional dyspepsia and/or irritable bowel syndrome, both of which characterized by irregular motor activity in the gut.

10

References

- Abell TL, Camilleri M, DiMagno EP, Hench VS, Zinsmeister AR, Malagelada JR. Long-term efficacy of oral cisapride in symptomatic upper gut dysmotility. *Dig Dis Sci* 1990; 36: 616-620.
- Agréus L, Talley N. Challenges in managing dyspepsia in general practice. *BMJ* 1997; 315: 1284-1288.
- Albibi R, McCallum RW. Metoclopramide: pharmacology and clinical application. *Ann Intern Med* 1983; 98; 86-95.
- Delattre M, Malesky M, Prinzie A. Symptomatic treatment of non-ulcer dyspepsia with cimetidine. *Curr Ther Res* 1985; 37: 980-991.
- Evans PR, Bennett EJ, Bak Y-T, Tennant CC, Kellow JE. Jejunal sensorimotor dysfunction in irritable bowel syndrome: Clin-

-11-

cal and psychosocial features. *Gastroenterology* 1996; 110: 393-404.

5 Gorard DA, Libby GW, Farthing MJG. 5-Hydroxytryptamine and human small intestinal motility: effect of inhibiting 5-hydroxytryptamine uptake. *Gut* 1994; 35: 496-500.

10 Gutniak MK, Juntti-Berggren L, Hellström PM, Guenifi A, Holst JJ, Efendic S. GLP-1 (glucagon-like peptide-1) enhances the insulinotropic effect of glibenclamide in NIDDM patients and in the perfused rat pancreas. *Diabetes Care* 1996; 19: 857-863.

Habener JF. The incretin notion and its relevance to diabetes. *Endocrinol Metab Clin North Am* 1994; 25: 25-31.

15 Kellow JE, Eckersley GM, Jones M. Enteric and central contributions to intestinal dysmotility in irritable bowel syndrome. *Dig Dis Sci* 1992; 37: 168-174.

20 Kellow JE, Gill RC, Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in irritable bowel syndrome. *Gastroenterology* 1990; 98: 1208-1218.

25 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology* 1987; 92: 1885-1893.

30 Kellow JE, Phillips SF, Miller LJ, Zinsmeister AR. Dysmotility of the small intestine in irritable bowel syndrome. *Gut* 1988; 29: 1236-1243.

Lind CD. Motility disorders in the irritable bowel syndrome. *Gastroenterol Clin North Am* 1991; 20: 279-295.

35 Locke GR, Talley NJ, Fett S, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux in the community. *Gastroenterology* 1997; 112: 1448-1456.

- Reboa G, Arnulfo G, DiSomma C et al. Prokinetic effect of cisapride on normal and reduced antroduodenal motility and reflexes. *Curr Ther Res* 1984; 36: 18-23.
- 5 Rösch W. Cisapride in non-ulcer dyspepsia. *Scand J Gastroenterol* 1987; 22: 161-164.
- Schmidt T, Hackelsberger N, Widmer R, Meisel C, Pfeiffer A, Kaess H. Ambulatory 24-hour jejunal motility in diarrheal predominant irritable bowel syndrome. *Scand J Gastroenterol* 10 1996; 31: 581-589
- Small PK, Loudon MA, Hau CM, Noor N, Cambell FC. Large-scale ambulatory study of postprandial jejunal motility in irritable bowel syndrome. *Scand J Gastroenterol* 15 1997; 32: 39-47.
- Talley NJ. Drug treatment of functional dyspepsia. *Scand J Gastroenterol* 1991; 26(suppl 182): 47-60.
- 20 Talley NJ, Zinsmeister AR, Schleck CD, Melton III LJ. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* 1992; 102: 1259-1268.
- Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 25 1993; 38: 665-673.

CLAIMS

1. The use of a gastrointestinal peptide hormone selected from the class consisting of glucagon-like peptide-1 (GLP-1) and derivatives thereof having anti-secretory effects and smooth muscle relaxatory properties in the gastrointestinal tract for the manufacture of a pharmaceutical composition for the treatment of functional dyspepsia and/or irritable bowel syndrome.
- 10 2. Use according to claim 1, wherein said GLP-1 or derivative thereof is combined with one or more other gastrointestinal peptide hormone(s) or derivative(s) in the pharmaceutical composition.
- 15 3. Use according to claim 2, wherein somatostatin is combined with GLP-1 in the pharmaceutical composition.
- 20 4. Pharmaceutical composition for the treatment of functional dyspepsia and/or irritable bowel syndrome characterized in that it comprises a combination of at least one member selected from the group consisting of GLP-1 and derivatives thereof having anti-secretory effects and smooth muscle relaxatory properties in the gastrointestinal tract with one or two more other gastrointestinal peptide hormone(s) and derivative(s) thereof having such effects and properties together with pharmacologically acceptable additives.
- 25 30 5. Pharmaceutical composition according to claim 4, characterized in that it comprises somatostatin in combination with GLP-1.
- 35 6. Method for the treatment of functional dyspepsia or irritable bowel syndrome or both in a human patient suffering therefrom which method comprises administering to said patient an effective amount of at least one member of the group consisting of GLP-1 and derivatives thereof having anti-

-14-

secretory effects and smooth muscle relaxatory properties in
the gastrointestinal tract.

7. Method according to claim 6, wherein GLP-1 is administered
5 in combination with somatostatin.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00997

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/26, A61K 38/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9701579 A2 (SANDOZ-PATENT-GMBH), 16 January 1997 (16.01.97), see page 19 --	1-5
A	WO 9803547 A1 (ONTARIO INC.), 29 January 1998 (29.01.98), see claim 17 -----	1-5

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
1 October 1999

Date of mailing of the international search report

08-10-1999

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Carolina Gómez Lagerlöf/EÖ
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00997

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 6-7
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00997

Claims 6-7 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/08/99

International application No.

PCT/SE 99/00997

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9701579 A2	16/01/97	AU 6515096 A CA 2222524 A CZ 9704196 A EP 0835263 A GB 9513224 D IL 122243 D NO 976064 A PL 323943 A SK 177097 A AU 690423 B AU 4729496 A BR 9607681 A EP 0813360 A GB 9600429 D	30/01/97 16/01/97 13/05/98 15/04/98 00/00/00 00/00/00 16/02/98 27/04/98 05/08/98 23/04/98 23/09/96 07/07/98 29/12/97 00/00/00
WO 9803547 A1	29/01/98	AU 3615797 A EP 0914341 A	10/02/98 12/05/99